

ABSTRACT

Many Gram-negative pathogens assemble adhesive structures on their surfaces that allow them to colonize host tissues and cause disease. Novel compositions for the prevention or inhibition of pilus assembly in Gram-negative pathogens are disclosed. Interacting with the binding site of pili subunits will negatively affect the chaperone/usher pathway which is one molecular mechanism by which Gram-negative bacteria assemble adhesive pili structures and thus prevent or inhibit pilus assembly. Additionally, novel compounds and compositions for interfering or preventing adhesion of pilated bacteria to host tissues are provided. Such compounds and compositions prevent or inhibit pili adhesion to host tissues by interacting with the mannose-binding domains on pilus adhesin subunits. Also provided are methods for the treatment or prevention of diseases caused by tissue-adhering pilus-forming bacteria by interaction with the binding between pilus subunits; the binding between pilus subunits and periplasmic chaperones; and the binding of a pilus adhesin to the host epithelial tissue. Also provided are pharmaceutical preparations capable of interacting with the binding between pilus subunits, between pilus subunits and periplasmic chaperones and between the pilus adhesin.

The present invention further relates to co-crystals of pilus chaperone-subunit co-complexes, detailed three dimensional structural information illustrating the interaction between pilus subunits and/or between a pilus subunit and a chaperone for a pilus chaperone-subunit co-complex and methods of utilizing the X-ray crystallographic data from such co-crystals to design, identify and screen for compounds that exhibit antibacterial activity.

The present invention also relates to machine readable media embedded with the three-dimensional atomic structure coordinates of pilus chaperone-subunit co-complex and subsets thereof.

09637216 "081100